Fluarix™ Tetra

Quadrivalent influenza vaccine (split virion, inactivated)

1. NAME OF THE MEDICINAL PRODUCT

Fluarix™ Tetra suspension for injection in pre-filled syringe
Influenza vaccine (split virion, inactivated)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Fluarix™ Tetra is an inactivated influenza vaccine (split virion), containing antigens (propagated in embryonated eggs) equivalent to the following types and subtypes:

A/California/7/2009 (H1N1)pdm09-like strain (A/Christchurch/16/2010, NIB-74xp);

A/Hong Kong/4801/2014 (H3N2)-like strain (A/Hong Kong/4801/2014, NYMC X-263B);

B/Brisbane/60/2008 - like strain (B/Brisbane/60/2008, wild type);

B/Phuket/3073/2013 - like strain (B/Phuket/3073/2013, wild type).

Each 0.5 ml vaccine dose contains 15 µg haemagglutinin of each of the recommended strains.

This vaccine complies with the World Health Organisation (WHO) recommendation (Northern Hemisphere) for the **2016/2017** season.

For the full list of excipients see *section 6.1*.

Fluarix™ Tetra may contain traces of Formaldehyde, Sodium Deoxycholate, Ovalbumin, Gentamicin Sulphate and Hydrocortisone. The maximum amount of Ovalbumin that may be present is not more than 0.05 micrograms per dose.

3. PHARMACEUTICAL FORM

Suspension for injection in pre-filled syringe.
The suspension is colourless and slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Fluarix™ Tetra is indicated for active immunisation of adults and children from 3 years of age for the prevention of influenza disease caused by the two influenza A virus subtypes and the two influenza B virus types contained in the vaccine.

The use of ***Fluarix™ Tetra*** should be based on official recommendations.

4.2 Posology and method of administration

Posology

Adults: 0.5 ml

Paediatric population

Children from 36 months onwards: 0.5 ml.

For children aged < 9 years, who have not previously been vaccinated, a second dose should be given after an interval of at least 4 weeks.

Vaccination should be carried out by intramuscular injection preferably into the deltoid muscle or anterolateral thigh (depending on the muscle mass).

Children less than 3 years: the safety and efficacy of ***Fluarix™ Tetra*** in children less than 3 years have not been established.

Method of administration

Immunisation should be carried out by intramuscular injection.

Precautions to be taken before handling or administering the medicinal product

For instructions for preparation of the medicinal product before administration, see *section 6.6.*

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1 or to any component that may be present as traces such as eggs (ovalbumin, chicken proteins), formaldehyde, gentamicin sulphate and sodium deoxycholate.

Immunisation should be postponed in patients with febrile illness or acute infection.

4.4 Special warnings and precautions for use

It is good clinical practice to precede vaccination by a review of the medical history (especially with regard to previous vaccination and possible occurrence of undesirable events) and a clinical examination.

As with all injectable vaccines, appropriate medical treatment and supervision should always be readily available in case of an anaphylactic event following the administration of the vaccine.

Antibody response in patients with endogenous or iatrogenic immunosuppression may be insufficient.

Fluarix™ Tetra is not effective against all possible strains of influenza virus. ***Fluarix™ Tetra*** is intended to provide protection against those strains of virus from which the vaccine is prepared and to closely related strains.

As with any vaccine, a protective immune response may not be elicited in all vaccinees.

Fluarix™ Tetra should under no circumstances be administered intravascularly.

As with other vaccines administered intramuscularly, ***Fluarix™ Tetra*** should be given with caution to individuals with thrombocytopenia or any coagulation disorder since bleeding may occur following an intramuscular administration to these subjects.

Syncope (fainting) can occur following, or even before, any vaccination especially in adolescents as a psychogenic response to the needle injection. This can be accompanied by several neurological signs such as transient visual disturbance, paraesthesia and tonic-clonic limb movements during recovery. It is important that procedures are in place to avoid injury from faints.

Interference with serological testing.
See *section 4.5.*

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. If ***Fluarix™ Tetra*** is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different injection sites.

Following influenza vaccination, false-positive results in serology tests using the ELISA method to detect antibodies against HIV1, Hepatitis C and especially HTLV1 have been observed. The Western Blot technique disproves the false-positive ELISA test results. The transient false-positive reactions could be due to the IgM response by the vaccine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Inactivated influenza vaccines can be used in all stages of pregnancy. Larger datasets on safety are available for the second and third trimester, compared with the first trimester; however, data from worldwide use of inactivated influenza vaccines do not indicate any adverse foetal and maternal outcomes attributable to the vaccine (see *Pre-clinical Safety Data*).

Breast-feeding

Fluarix™ Tetra may be used during breast-feeding.

Fertility

No fertility data are available.

4.7 Effects on ability to drive and use machines

Fluarix™ Tetra has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In two clinical studies, healthy adults 18 years of age and older and healthy children 3 to 17 years of age were administered ***Fluarix™ Tetra*** (more than 3,000 adults and 900 children) or

GlaxoSmithKline trivalent influenza vaccine, ***Fluarix™*** (more than 1,000 adults and 900 children). Similar rates of solicited adverse events were observed in recipients of ***Fluarix™ Tetra*** and ***Fluarix™***.

Adverse reactions reported for ***Fluarix™ Tetra*** are listed per dose according to the following frequency categories:

Very common (≥1/10);
Common (≥1/100 to <1/10);
Uncommon (≥1/1,000 to <1/100);
Rare (≥1/10,000 to <1/1,000);
Very rare (<1/10,000)

Frequency	**Adverse reactions**
Clinical trials	
Very common	irritability[1], myalgia, injection site pain, fatigue
Common	appetite loss[1], drowsiness[1], headache, gastrointestinal symptoms (including nausea, vomiting, diarrhoea and/or abdominal pain), arthralgia, injection site redness[4], injection site swelling[4], shivering, fever
Uncommon	dizziness[2], rash[3], injection site hematoma[2], injection site pruritus
[1]reported as a solicited symptom in subjects less than 6 years of age [2]reported in adult subjects [3]reported in subjects 3 years to 17 years of age [4]very common in subjects 3 years to 17 years of age	
Adverse reactions additionally reported in previous *Fluarix™* trials:	
Common	Sweating, injection site induration
Post-marketing experience The following adverse events that have been observed for ***Fluarix™*** during post-marketing surveillance may occur in patients receiving ***Fluarix™ Tetra*** post-approval, as all three of the influenza strains contained in ***Fluarix™*** are included in ***Fluarix™ Tetra***.	
Rare	transient lymphadenopathy, allergic reactions (including anaphylactic reactions), neuritis, acute disseminated encephalomyelitis, Guillain-Barré syndrome*, urticaria, pruritus, erythema, angioedema, influenza-like illness, malaise *Spontaneous reports of Guillain-Barré syndrome have been received following vaccination with ***Fluarix™***; however, a causal association between vaccination and Guillain-Barré syndrome has not been established.

4.9 Overdose

Insufficient data are available.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Influenza vaccine, ATC Code: J07BB02

Mechanism of action

Fluarix™ Tetra provides active immunisation against four influenza virus strains (two A subtypes and two B types) contained in the vaccine and induces humoral antibodies against the haemagglutinins. These antibodies neutralise influenza viruses.

Specific levels of hemagglutination-inhibition (HI) antibody titer post-vaccination with inactivated influenza virus vaccines have not been correlated with protection from influenza illness but the HI antibody titers have been used as a measure of vaccine activity. In some human challenge studies, HI antibody titres of ≥1:40 have been associated with protection from influenza illness in up to 50% of subjects.

Pharmacodynamic effects

Immunogenicity of *Fluarix™ Tetra* versus *Fluarix™*

Clinical studies performed in adults (D-QIV-001 and D-QIV-008) and in children 3 years to 17 years of age (D-QIV-003) assessed the non-inferiority of ***Fluarix™ Tetra*** versus ***Fluarix™*** for HI Geometric mean antibody titer (GMT) at Day 21 (for adults) and at Day 28 (for children) and HI seroconversion rate (4-fold rise in reciprocal titer or change from undetectable [< 10] to a reciprocal titer of ≥ 40).

In all studies, the immune response elicited by ***Fluarix™ Tetra*** against the three strains in common was non-inferior to ***Fluarix™***. ***Fluarix™ Tetra*** elicited a superior immune response against the additional B strain included in ***Fluarix™ Tetra*** compared to ***Fluarix™***.

Adults 18 years of age and older

In clinical study D-QIV-008, approximately 1,800 adults 18 years of age and older received a single dose of ***Fluarix™ Tetra*** and approximately 600 subjects received a single dose of ***Fluarix™*** (Table 1).

Table 1: Post-vaccination GMT and seroconversion rates:

Adults 18 years of age and older	***Fluarix™ Tetra*** N=1809	***Fluarix™*** [1] N=608
	GMT (95% confidence interval)	
A/H1N1	201.1 (188.1;215.1)	218.4 (194.2;245.6)
A/H3N2	314.7 (296.8;333.6)	298.2 (268.4;331.3)
B (Victoria)[2]	404.6 (386.6;423.4)	393.8 (362.7;427.6)
B (Yamagata)[3]	601.8 (573.3;631.6)	386.6 (351.5;425.3)
	Seroconversion rate (95% confidence interval)	
A/H1N1	77.5% (75.5;79.4)	77.2% (73.6;80.5)
A/H3N2	71.5% (69.3;73.5)	65.8% (61.9;69.6)
B (Victoria)	58.1% (55.8;60.4)	55.4% (51.3;59.4)
B (Yamagata)	61.7% (59.5;64.0)	45.6% (41.6;49.7)

[1]containing A/H1N1, A/H3N2 and B (Victoria lineage)
[2]recommended strain by WHO during the season 2010-2011
[3]additional B strain contained in ***Fluarix™ Tetra*** recommended in season 2008-2009

Post-vaccination seroprotection rates (Day 21 reciprocal titer of ≥ 40) for ***Fluarix™ Tetra*** were 91.3% against A/H1N1, 96.8% against A/H3N2, 98.8% against B (Victoria) and 91.8% against B (Yamagata).

In clinical study D-QIV-001 (vaccine composition of 2007-2008 season), post-vaccination seroprotection rates for ***Fluarix™ Tetra*** were 92.3% against A/H1N1, 97.1% against A/H3N2, 97.1% against B (Victoria) and 98.1% against B (Yamagata).

Children 3-17 years of age

In clinical study (D-QIV-003), approximately 900 children from 3-17 years of age received one or two doses of ***Fluarix™ Tetra*** or ***Fluarix™***, respectively (Table 2).

Table 2: Post-vaccination GMT and seroconversion rates:

Children 3 years to 17 years of age	***Fluarix™ Tetra*** N=791	***Fluarix™*** [1] N=818
	GMT (95% confidence interval)	
A/H1N1	386.2 (357.3;417.4)	433.2 (401.0;468.0)
A/H3N2	228.8 (215.0;243.4)	227.3 (213.3;242.3)
B (Victoria)[2]	244.2 (227.5;262.1)	245.6 (229.2;263.2)
B (Yamagata)[3]	569.6 (533.6;608.1)	224.7 (207.9;242.9)
	Seroconversion rate (95% confidence interval)	
A/H1N1	91.4% (89.2;93.3)	89.9% (87.6;91.8)
A/H3N2	72.3% (69.0;75.4)	70.7% (67.4;73.8)
B (Victoria)	70.0% (66.7;73.2)	68.5% (65.2;71.6)
B (Yamagata)	72.5% (69.3;75.6)	37.0% (33.7;40.5)

[1]containing A/H1N1, A/H3N2 and B (Victoria lineage)
[2]recommended strain by WHO during the season 2010-2011
[3]additional B strain contained in ***Fluarix™ Tetra*** recommended in season 2008-2009

Post-vaccination seroprotection rates for ***Fluarix™ Tetra*** were 96.6% against A/H1N1, 98.0% against A/H3N2, 97.3% against B (Victoria) and 99.2% against B (Yamagata).

5.2 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of acute toxicity, local tolerance, repeated dose toxicity and reproductive/developmental toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride, disodium phosphate dodecahydrate, potassium dihydrogen phosphate, potassium chloride, magnesium chloride hexahydrate, α-tocopheryl hydrogen succinate, polysorbate 80, octoxinol 10 and water for injections.

Hydrocortisone, gentamicin sulfate, ovalbumin, formaldehyde and sodium deoxycholate are present as residuals from the manufacturing process.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

The expiry date is indicated on the label and packaging.

6.4 Special precautions for storage

Store in a refrigerator (2°C to 8°C).

Do not freeze.

Store in the original package in order to protect from light.

6.5 Nature and contents of the container

0.5 ml suspension in prefilled syringe (Type I glass) with a plunger stopper (grey butyl rubber) with fixed or separate or without needles in the following pack sizes:

- with fixed needle: pack sizes of 1 or 10
- with 1 separate needle: pack sizes of 1 or 10
- with 2 separate needles: pack size of 1
- without needle: pack sizes of 1 or 10

The needle type(s) that may be supplied in the pack are: 23G 1", 25G 5/8" and 25G 1".

Not all presentations are available in every country.

6.6 Special precautions for disposal and other handling

The vaccine should be allowed to reach room temperature before use.

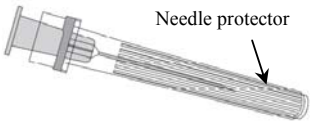
The vaccine presents as a colourless to slightly opalescent suspension.

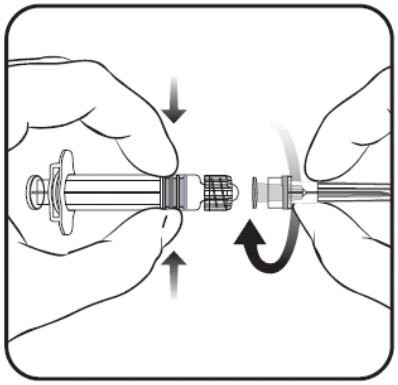
The syringe should be shaken and inspected visually for any foreign particulate matter and/or variation of physical aspect prior to administration. In the event of either being observed, discard the vaccine.

Instructions for administration of the vaccine presented in pre-filled syringe without a fixed needle

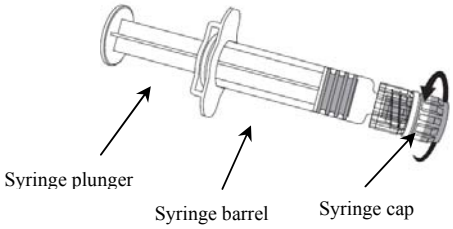
To attach the needle to the syringe, refer to the below drawing. However, the syringe provided with ***Fluarix™ Tetra*** might be slightly different (without screw thread) than the syringe described in the drawing. In that case, the needle should be attached without screwing.

Needle





Syringe



1. Holding the syringe **barrel** in one hand (avoid holding the syringe plunger), unscrew the syringe cap by twisting it anticlockwise.
2. To attach the needle to the syringe, twist the needle clockwise into the syringe until you feel it lock. (see picture)
3. Remove the needle protector, which on occasion can be a little stiff.
4. Administer the vaccine.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Fluarix is a trademark of the GSK group of companies.

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Manufacturer:
GlaxoSmithKline Biologicals, Branch of SmithKline Beecham Pharma GmbH & Co. KG, Dresden, Germany

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